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| EXAMINER | |
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| ROONEY, NORA MAUREEN | |
| ART UNIT | PAPER NUMBER |
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/719,553 | IPSEN ET AL. | |
| | Examiner | Art Unit | |
| | NORA M. ROONEY | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *36-96* is/are pending in the application.

4a) Of the above claim(s) *44-65 and 74-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-43 and 66-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's response filed on 02/06/2009 is acknowledged.

2. Claims 36- 96 are pending.

3. Claims 44-65 and 74-96 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

4. Claims 36-43 and 66-73 are currently under examination as they read upon a recombinant mutant Bet v 1 allergen and the 'Triple-patch' mutant of species of 'ix.' in claim 37.

5. In view of Applicant's response filed on 02/06/2009, the following rejections are maintained.

### *Double Patenting*

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

*Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 36-43 and 66-73 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 of copending Application No. 10/001,245. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims arrive at similar allergenic variants, and by what appears to the Examiner to be the same method of selection, or if not, by an obvious variant thereof. Specifically, Claims 1-22, 25-26, 28, 35, 37-39, 64 and 66-85 teach a mutant Bet V1 allergen with 1 or more substitutions, wherein said substitutions occur at many amino acid residues that are identical positions between the '245 application and the instant application, such as those recited in copending claim 22 and instant claim 37. Claim 22 of the '245 application recites substituting unspecified amino acids at one or

more given positions, whereas the instant application recites specific substitutions at some of the same positions. However, on page 29 of the '245 specification in example 2595, the identical 'triple patch' mutant species of instant claim 37 is disclosed. Therefore, the claims are not patentably distinct from one another for the same reasons as set forth in the Office Action mailed on 08/06/2008.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments submitted on 02/06/2009 have been fully considered, but are not found persuasive.

Applicants argue:

> "Applicants confirm that the '245 application has not issued as a patent. Accordingly, Applicants are not required to respond to the instant rejection at this time.
>
> It is noted that the instant application was filed prior to the '245 application. Thus, according to the rules of practice, if the obviousness-type double patenting rejection is the last remaining rejection in the instant application and rejections remain in the '245 application, the obviousness-type double patenting rejection of the instant claims should be withdrawn and the application permitted to issue as a patent without the filing of a terminal disclaimer. *See* MPEP §804.I.B.1."

It is the Examiner's position that the rejection stands until the rejected claims are cancelled or until a terminal disclaimer is filed. In addition, this is not the last remaining rejection. Accordingly, the rejection is maintained.

*Claim Rejections - 35 USC § 112*

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 36, 38-43 and 66-73 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a recombinant mutant allergen from birch pollen major allergen Bet v a of SEQ ID NO:37 having the amino acid substitutions recited in claim 37.

However, applicant is not in possession of: a recombinant mutant Bet v 1 allergen derived from a naturally-occurring Bet v 1 allergen from the order Fagales, said recombinant mutant Bet v 1 allergen having: (a) a substitution of **a solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the order Fagales**, said substitution occurring in **a B-cell epitope of said naturally-occurring Bet v 1 allergen**; (b) reduced specific IgE binding compared to said naturally-occurring Bet v 1 allergen from which it is derived; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring Bet v 1 allergen** of claim 36; wherein said **solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%** of claim 38; wherein **said conserved solvent-accessible amino**

**acid residue is conserved with more than 70% identity among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen originates** of claim 39; wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5% of claim 40; wherein **the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å** in claim 41; wherein **said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen**; wherein said **solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen is substituted with an amino acid that is not conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally occurring Bet v 1 allergen occurs**; or a recombinant mutant allergen derived from a naturally-occurring allergen within the order Fagales that is **homologous to Bet v 1 allergen**, said recombinant mutant allergens having: (a) **a substitution of a solvent-accessible amino acid residue that is covered among homologous allergens within the taxonomic order Fagales**, said **substitution occurring in a B-cell epitope of said naturally-occurring allergen**; (b) reduced specific IgE binding compared to said naturally-occurring allergen; and (c) **an α-carbon backbone tertiary structure that is preserved as compared to the α-carbon backbone tertiary structure of said naturally-occurring allergen** of claim 66; wherein said allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than .1 when compared to an amino

acid sequence of SEQ ID NO:37 of claim 67; wherein **said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%** of claim 68; wherein **said conserved solvent-accessible amino acid residue is conserved with more than 70% identity among homologous allergens within the taxonomic order from which said naturally-occurring allergen originates** of claim 69; wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5% of claim 70; wherein **the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å** of claim 71; wherein **said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å$^2$ of the surface of said naturally-occurring allergen** of claim 72; or wherein **said solvent-accessible amino acid residue that is conserved among homologous allergens within the taxonomic order from which said naturally-occurring allergen occurs** for the same reasons as set forth in the Office Action mailed on 08/06/2008.

Applicant's arguments submitted on 02/06/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> "The Examiner has failed to respond substantively to the April 30 response. The Examiner has acknowledged the factors set out in the April 30 response by copying Applicants' analysis into the latest Office Action. *See* pages 7-10. Similarly, in the latest Office Action on pages 5-7, the Examiner has copied and recited each of the limitations set forth respectively in claims 36, 38-43 and 66-73. The Examiner again quotes the respective claim limitations on page 11 of the Office Action. Lengthy and verbatim repetition of claim limitations and Applicants' argument, however, does not equate with "a fact-based inquiry that [depends] on the nature of the invention" *(Carnegie Mellon Univ.,* 541 F.3d at 1122) that is "applied in the

context of the particular invention and the state of the knowledge" *(Capon,* 418 F.3d at 1357). In view of the Examiner's failure to substantively consider Applicants' detailed consideration of the factors that the USPTO acknowledges "should be considered" in determining written description, the Examiner's assertion that the specification fails to provide adequate written description for the claims is mere conclusion, unsupported by facts. Because the written description rejection is by facts, it should be withdrawn.

Moreover, the sole factual assertion by the Examiner is mistaken. The Examiner thus asserts, "[t]here is also no indication in the specification as to how the particular point mutation strategy relates to the claimed functions such that one would know how to change the function by aparticular mutation." Office Action at page 12. Contrary to the Examiner's assertion, the specification when read in view of the knowledge in the art provides an abundance of guidance on making the claimed recombinant mutant Bet v 1 allergens.

It was general knowledge in the art at the time the application was filed that allergens with reduced IgE binding could be produced by site-directed mutagenesis. *See* specification and cited references at page 7, line 26, et seq. The specification further discloses that the amino acids available for antibody binding are located on the surface of allergens *(see* specification at page 19, lines 30-36). The functional characteristic of reduced IgE binding flows directly from (i.e., is "coupled with") the known property of IgE epitopes to be present on the surface of allergens, particularly in conserved patches on the allergen surface, and the disclosed and well known correlation that disrupting IgE epitopes will reduce IgE binding. The state of the art was such that it was known, for example, that Bet v 1 allergens include IgE epitopes, that they reside in surface patches, that Bet v 1 proteins from the order Fagales share a high level of identity and exhibit cross reactivity, and that substitution of amino acids on the surface of Bet v 1 allergens could disrupt IgE epitopes and lower IgE binding.

The specification sets forth that: The major birch pollen allergen Bet v 1 (SEQ ID NO: 37) shows about 90% amino acid sequence identity with major allergens from pollens of taxonomically related trees, i.e. *Fagales* (or instance hazel and hornbeam) and birch pollen allergic patients often show clinical symptoms of allergic cross-reactivity towards these Bet v 1 homologous proteins.

Specification at page 24, lines 8-14. Based on the level of skill in the art at the time the application was filed, a worker of ordinary skill in the art would have recognized that the high degree of identity among Bet v 1 homologous proteins from the order Fagales and the finding that birch pollen allergic patients exhibited symptoms of allergic cross-reactivity towards these homologous proteins indicates that Bet v 1 homologous proteins from the order Fagales have highly similar primary sequences and three-dimensional structures, indicating that the features that are set forth above and which indicate that the Applicants had possession of the mutant allergens for Bet v 1 proteins from the order Fagales also hold for the broader genus of recombinant mutant allergens of Bet v 1 homologous proteins from the order Fagales. Thus, the specification provides written description for the full scope of recombinant mutant Bet v 1 allergens from the order Fagales. *See* claims 36 and 66.

The specification read in light of the knowledge of the state of the art also provides written description for each of the particular features recited the claims. Thus, the general level of skill and knowledge in the art would readily allow one of ordinary skill in the art to use the known crystal structure of Bet v 1 and/or sequence alignment of Bet v 1 sequences to identify amino acids that have a solvent accessibility of 20% (claims 38 and 68), identify amino acids that are conserved with 70% identity among Bet v 1 allergens from the order Fagales (claims 39 and 69), wherein a conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400A of the surface of said naturally-occurring Bet v 1 allergen (claims 42 and 72), wherein the solvent-accessible amino acid residue that is conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen is substituted with an amino acid that is not conserved among Bet v 1 homologous allergens within the taxonomic order from which said naturally-occurring Bet v 1 allergen occurs (claims 43 and 73) and wherein said allergens homologous to Bet v 1 have an amino sequence that yields a BLAST probability of less than 0.1 when compared to an amino acid sequence of SEQ ID NO: 37

(claim 67). The specification further provides extensive guidance on tests that can be used to determine with recombinant Bet v 1 allergens have IgE binding reduced by at least 5%, compared to the naturally-occurring Bet v 1 allergen from which it is derived (claims 40 and 70) and wherein average root mean square deviation of the atomic coordinates comparing the m-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergen is less than 2,~ (claims 41 and 71).

Thus, the Applicants were in possession of the complete subject matter of claims 36, 38-43 and 66-72.

The Examiner, moreover, explicitly contradicts the assertion that there is "no indication in the specification as to how the particular point mutation strategy relates to the claimed functions such that one would know how to change the function by a particular mutation," by stating that "one [can] figure out what allergen mutants are encompassed by the instant recitation and make them." One can figure out "how to change [Bet v 1] function by a particular mutation" because the specification details precisely which amino acids are to be mutated, i.e., solvent- accessible amino acid residues that are conserved among Bet v 1 homologous allergens within theorder Fagales *(see* specification at page, 14, line 34 - page 15, line 4), preferably wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400,~ of the surface of said naturally-occurring Bet v 1 allergen (specification at page, 15, lines 6-11).

The structure of Bet v 1 was known at the time the application was filed and Bet v 1 allergens are highly conserved. There is no rule that the Applicants provide description of the precise mutant amino acids in the claimed recombinant Bet v 1 mutants. *Falkner,* 448 F.3d at 1366. Applicants are entitled to "flexibility" in how they claim their invention. *Univ. of Rochester,* 358 F.3d 916 at 927-928. Thus, in view of the high level of skill in the art, the predictable position of IgE epitopes among Bet v 1 allergens, and the predictable consequence of mutating amino acid residues within these epitopes (i.e., reduction of IgE binding with retention of native structure) the guidance provided in the specification suffices to describe to one of ordinary skill in the art the full complement of amino acids that can be mutated to arrive at the claimed Bet v 1 allergen mutants.

Certain additional points raised by the Examiner are addressed as follows.

In support of the instant rejection, the Examiner cites in *Ex parte Kubin* (83 U.S.P.Q.2d 1410 (BPAI 2007). In *Kubin,* the Board upheld the rejection of a claim directed to isolated polynucleotides encoding polypeptides that (1) "are at least 80% identical to amino acids 22-221 of SEQ ID NO: 2" (i.e., the amino acid sequence for the extracellular domain of the protein natural killer cell activation inducing ligand ("NAIL") lacking the NAIL signal sequence) and (2) which bind to the glycoprotein CD 48. *Id.* at 1417. The Board found that the Applicant had failed to describe what domains of within amino acids 22-221 of SEQ ID NO: 2 correlated with the function of binding CD 48, and thus the Applicant had not described which NAIL amino acids could be varied and still maintain CD 48 binding. *Id.* The Board found that in the absence of a structure-function correlation, the claim merely defined the invention by function, which was not sufficient to satisfy the written description requirement.

The facts in Kubin differ significantly from the facts of the instant case. In *Kubin,* the Applicant failed to provide any features of amino acids 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. Nor did the start of the art provide any features of 22-221 of SEQ ID NO: 2 that correlated with binding to CD 48. In the instant case, the three-dimensional structure of Bet v 1 was known when the application was filed, as was the sequence of other Bet v 1 allergens, and the specification discloses that details precisely which amino acids are to be mutated, i.e., solvent- accessible amino acid residues that are conserved among Bet v 1 homologous allergens within the order Fagales, preferably wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400A of the surface of said naturally-occurring Bet v 1 allergen. Furthermore it was highly predictable that mutations in surface-exposed epitopes would have the desired effect of reducing IgE

binding while retaining native structure of a Bet v 1 mutant. Thus, the state of the art pertaining to the instant invention was significantly more highly advance that the state of the art pertaining to Kubin's invention, the instant application provides significantly more guidance as to which features of the protein in question are important for function, and the effect of mutations on the function of the instantly claimed Bet v 1 mutant allergens (IgE binding) is more predictable than the function of mutations in the NAIL proteins disclosed in Kubin. Thus, the basis of the Board's decision in Kubin does not apply to the instant claims. Lastly, the Examiner characterizes each of the properties called for in the claims as "functional limitations." See Office Action at, e.g., page 11. These purported "functional limitations include "reduced specific IgE binding," "occurring in a B-cell epitope," "a-carbon backbone tertiary structure that is preserved," "solvent accessibility of at least 20%," "average root o mean square deviation...of less than 2 A," "within a patch of conserved amino acids connected over o at least 400A of the surface [of naturally occurring Bet v 1]," and "an amino acid sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37." With two exceptions discussed immediately below, the characterization of these properties as "functional limitations" is mistaken. Each of the other properties is a physical property that flows directly from the (highly conserved) sequence of Bet v 1 allergens. Thus, amino acids with a "solvent accessibility of at least 20 .... within a patch of conserved amino acids connected over at least 400A of the surface [of naturally occurring Bet v 1]" are immediately apparent to one of ordinary skill in the art by simply examining the three dimensional structure of Bet v 1 (or other Bet v 1 allergen modeled on Bet v 1). Identification of "an amino acid sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37" is even more straight forward--one of ordinary skill in the art need only use well known methods to compare Bet v 1 allergen sequences. With respect to the properties of "a-carbon backbone tertiary structure that is preserved" and "average root mean square deviation...of less than 2 A," these are features of a protein that has folded in a native three-dimensional structure, which flows directly from the Bet v 1 sequence (and which is conserved among Bet v 1 allergens). Moreover, as demonstrated by the examples set forth in the specification, Bet v 1 mutants bearing the mutations called for in the claims retain a native structure.

In short, each of the properties discussed above is physical characteristic that is derived directly from the conserved sequences of Bet v 1 allergens. The conserved sequence of Bet v 1 allergens provides a "common partial structural feature" for the claimed Bet v 1 mutants.

Finally, as set forth above, the specification provides ample guidance on Bet v 1 the position of B-cell epitopes on the surface of Bet v 1 allergens and how to predictably make mutations in the amino acids present in these epitopes such that IgE binding is reduced. Accordingly, the specification provides description of the amino acids that can be mutated so as to provide adequate written description for to functional limitations of "reduced specific IgE binding" and "occurring in a B-cell epitope."

It remains the Examiner's position that the specification has not adequately described the genus of allergen mutants encompassed by the instant claim recitations. Contrary to Applicant's assertion the arguments set forth by the Examiner on 08/06/2008 are a substantive response. Again, it remains the Examiner's position that the specification does not disclose a correlation between structure of the allergen and function (reduced specific IgE binding) and in this case functional limitations ("occurring in a B-cell epitope" and "α-carbon backbone tertiary structure

that is preserved" of claim 36 "wherein said solvent accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 38; "wherein the specific IgE binding of said mutant Bet v 1 allergen compared to said naturally-occurring Bet v 1 allergen from which it is derived is reduced by at least 5%" of claim 40; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant Bet v 1 allergen and said naturally-occurring Bet v 1 allergens is less than 2 Å" in claim 41; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 Å of the surface of said naturally-occurring Bet v 1 allergen" of claim 42; "an amino sequence that yields a BLAST probability of less than .1 when compared to an amino acid sequence of SEQ ID NO:37" of claim 67; "wherein said solvent-accessible conserved amino acid residue has a solvent accessibility of at least 20%" of claim 68; "wherein the specific IgE binding of said mutant allergen compared to said naturally occurring allergen from which it is derived is reduced by at least 5%" of claim 70; "wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of said recombinant mutant allergens and said naturally-occurring allergen is less than 2 Å" of claim 71; "wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400 $Å^2$ of the surface of said naturally-occurring allergen" of claim 72) such that a skilled artisan would have known what modification to make to the Bet v 1 allergens to attain the claimed function and functional limitations. "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" In re Kubin, of record, at page 16. In this instant case Applicants have not provided sufficient guidance as to

what mutation or combination of mutations will result in the claimed functions and functional limitations. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" *supra*, at page 17.

The above response is not a mere conclusion unsupported by facts because the lack of written description is a fact, given Applicant's disclosure in the specification. It is difficult to assert facts that are not present. The lack of facts in the specification is a fact in and of itself that has been asserted by the Examiner. So, the fact remains that Applicant has not described a correlation between the structure of the allergen mutants and the functional limitations.

Contrary to Applicant's assertion, "the art" does not describe the functions asserted in the claims. Applicant is encouraged to submit evidence of the functional limitations of Bet v 1 allergens recited being well known in the art.

The Examiner agrees with Applicant's assertion that it was general knowledge in the art at the time the application was filed that allergens with reduced IgE binding could be produced by site-directed mutagenesis. But, that's not what Applicant is claiming. Applicant is claiming allergen mutants with functional characteristics which are not well known in the art and allergen mutants wherein the mutations are made to amino acid residues of "homologous" allergens. There is simply no written description of the genus of such allergen mutants encompassed in the specification.

The Examiner has not contradicted the assertion that there is "no indication in the specification as to how the particular point mutation strategy relates to the claimed functions such that one would know how to change the function by a particular mutation," by stating that "one [can]

figure out what allergen mutants are encompassed by the instant recitation and make them." Whether one can "figure them out" and whether the specification has disclosed the relationship are two different things altogether. Written description is not about whether one can figure it out. Written description is about whether it has been described in the Application. One of ordinary skill in the art might be able to experimentally figure out the genus, but that does not change the fact that Applicant has not adequately described them.

In the instant case, the three-dimensional structure of Bet v 1 might have been known, but which amino acids are "solvent- accessible amino acid residues that are conserved among Bet v 1 homologous allergens within the order Fagales preferably wherein said conserved solvent-accessible amino acid residue is within a patch of conserved amino acid residues connected over at least 400A of the surface of said naturally-occurring Bet v 1 allergen" was not known. Contrary to Applicant's assertion, it was not highly predictable what mutations in surface-exposed epitopes would have the desired effect of reducing IgE binding while retaining native structure of a Bet v 1 mutant. Again, Applicant is encouraged to submit additional data to support the contention that these factors were known at the time of invention. The Examiner is also not persuaded regarding Applicant's assertion that the instant claims are distinguished over those of Kuby, especially with regard to Applicant's assertion that the level of skill in the art in the instant case is somehow higher. The level of skill in the art in both cases is equivalent.

Applicant's argument regarding the Examiner's characterization of the claim recitations as functional limitation is also unpersuasive. The specification has not adequately described the genus of allergen mutants encompassed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 15, 2009

Nora M. Rooney

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